and

(ii) a control comprising an amount of an isolated nucleic acid as in any one of claims 1 or 4 for comparing to a measured value of hybridization of said nucleic acid agent to said isolated nucleic acid in (i).

REMARKS

Specification

Page 12 of the specification is amended to eliminate all references to hyperlinks (lines 18 and 19 of the original disclosure).

No new matter has been added.

Claims

Claims 1-11 and 26 are pending in the application.

Claim 1 is amended for clarity and now includes language directed to the function of the polypeptide encoded by the nucleic acid, specifying that the polypeptide encoded "stimulates the growth of lens epithelial cells." Support for this amendment can be found throughout the application and at least on pages 48 and 49 (Examples 6 and 7). Claim 1 is further amended to include in proper form the hybridization buffer ingredients.

Claim 4 is amended for clarity. The antecedent basis for "sequence group" has been corrected. The wording "fragments of (1) and (2)" has also been eliminated. Reference in the claim to amino acid sequences having SEQ ID NO: 14, 15, and 16 has been corrected so that the term "complement" only refers to the nucleic acid having a sequence set forth as SEQ ID NO: 21.

Claim 6 is amended for clarity. Language directed to a fragment size less than, and including, 20 nucleotides is eliminated. The term "unique" is also introduced to establish/clarify the appropriate antecedent basis of the term with respect to its corresponding phrase in claim 4.

Claim 7 is amended for clarity and now includes language directed to a structural feature of the polypeptide ("the polypeptide shares at least 75% amino acid identity to SEQ ID NO.: 2"), and further clarifies that the "fragment thereof" is a "fragment of the polypeptide thereof."

Claim 26 is amended for clarity specifying that it is "the package" that "contains" the nucleic acid agent. Claim 26 is further amended to replace the language "selectively binds" with "hybridizes," a term commonly used in connection with nucleic acid art. Claim 26 is further amended to be in proper form with respect to the multiple dependency conflict.

No new matter has been added.

Rejection of Claims Under 35 U.S.C. §112, first paragraph

Claims 1, 8, 10 and 26 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claim 1 as amended specifically recites that nucleic acid molecules of claim 1 code for polypeptides which stimulate the growth of lens epithelial cells. An essential feature of the claimed invention are isolated nucleic acids that hybridize to SEQ ID NO: 1, under stringent conditions, and encode polypeptides which stimulate the growth of lens epithelial cells. Thus, claim 1 as amended is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO: 1 and must encode a protein with a specific activity. Hybridization techniques using a known DNA as a probe under stringent conditions were conventional in the art at the time of filing. The search of the prior art indicates that SEQ ID NO: 1 is novel and unobvious. There is a single species disclosed (a molecule consisting of SEQ ID NO: 1) that is within the scope of the claimed genus. There is actual reduction to practice of the disclosed species. A person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the stringent hybridization conditions set forth in the claim (highly stringent according to standards in the art) yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that Applicants was in possession of the claimed invention. It is therefore Applicants' belief that the claimed invention is adequately described.

In view of the foregoing amendments and arguments, Applicants respectfully request withdrawal of the foregoing rejections of claims 1, 8, 10 and 26 under 35 U.S.C. §112, first paragraph.

Claim 7 stands rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner, "the specification, while being enabling for a polynucleotide encoding the amino acids

sequence of SEQ ID NO: 2, does not reasonably provide enablement for a nucleic acid molecule encoding a polypeptide that binds a human antibody." The Examiner further states that "there are no structural or functional limitations to the human antibody."

Claim 7 as amended now includes language directed to a structural feature of the polypeptide to which a human antibody binds. According to amended claim 7, "the [encoded] polypeptide shares at least 75% amino acid identity to SEQ ID NO.: 2." Thus, it is Applicants' belief that a structural relationship between the human antibody and the exemplified LEDGF (SEQ ID NO.: 2) now exists, rendering the Examiner's rejection moot.

In view of the foregoing amendments and arguments, Applicants respectfully request withdrawal of the foregoing rejections of claim 7 under 35 U.S.C. §112, first paragraph.

Claims 4-7, 9, 11, 26 stand rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner, "the specification, while being enabling for an isolated nucleic acid molecule consisting of a fragment of SEQ ID NO: 1, wherein said fragment is between 20 and 3360 nucleotides long, does not reasonably provide enablement for an isolated nucleic acid molecule that is a fragment of SEQ ID NO: 1 between 20 and 3360 nucleotides in length which is not identical to 'fragments of (1) and (2),' and that "there are no limitations to 'fragments of (1) and (2)'."

Claim 4 as amended eliminates the recitation of "fragments of (1) and (2)," thus rendering the Examiner's rejection moot.

In view of the foregoing amendments, Applicants respectfully request withdrawal of the foregoing rejections of claims 4-7, 9, 11, 26, under 35 U.S.C. §112, first paragraph.

Claim Objections

Claim 26 is objected to as being in improper form because, according to the Examiner, "a multiple dependent claim should refer to other claims in the alternative."

Claim 26 as amended is believed to be in proper multiple dependent form and the Examiner is respectfully requested to withdraw his objection to this claim.

Claims 5 and 6 are objected to as being in improper dependent form for failing to further limit the subject matter of a previous claim.

With respect to claim 6, Applicants agree with the Examiner and have amended the claim to eliminate reference to nucleotide fragments less than 20 nucleotides in length. Claim 6 as amended is

believed to be in proper dependent form and the Examiner is respectfully requested to withdraw the objection to this claim.

With respect to claim 5, Applicants respectfully disagree. Claim 5 imposes a restriction to the length of the sequence of contiguous nucleotides of claim 4 that are not identical to SEQ ID NO.: 21 or to complements of SEQ ID NO.: 21. Claim 5 is believed to be in proper dependent form and the Examiner is respectfully requested to withdraw the objection to this claim.

Rejection of Claims Under 35 U.S.C. §112 (second paragraph)

Claims, 1, 4, 5, 7, 6, 8, and 26, stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the invention.

According to the Examiner, "claim 1 is indefinite because it is unclear if the limitations in parentheses are merely exemplary of a hybridization buffer or it they are intended to limit the hybridization buffer.

Claim 1 as amended includes the "comprising" language for the hybridization buffer ingredients, as suggested by the Examiner, thus obviating the Examiner's rejection. In view of the Applicants' amendments, Applicants respectfully request withdrawal of the Examiner's rejection of Claim 1, under 35 U.S.C. §112, second paragraph.

According to the Examiner, "claims 1 and 4 are indefinite over the recitation of 'complements of' because it is unclear if a polynucleotide that is the complement, a polynucleotide that is a portion of the complement, or a polynucleotide comprising either continuous or discontinuous complements is intended."

Respectfully, Applicants disagree. The term "complements" is a term well known in the art and it refers to the complementary strand of a nucleic acid molecule. It is a continuous strand of the bases and, it is of identical length to the number of bases in the opposite strand (e.g., the "anti-sense" strand). This is the meaning also intended by Applicants: a continuous strand of bases that complements, for example, the hybridizing strand in its entirety. In view of the Applicants' arguments, Applicants respectfully request withdrawal of the Examiner's rejection of Claims 1 and 4, under 35 U.S.C. §112, second paragraph.

According to the Examiner, "claim 4 is indefinite over the recitation of "complements of" SEQ ID NO: 14, 15 or 16 because SEQ ID NO: 14, 15 and 16 are amino acid sequences and the specification fails to define a complement of an amino acid sequence."

Claim 4 as amended eliminates reference to amino acid sequences (e.g., SEQ ID NO: 14, 15, and 16), and the term "complement" now only refers to the nucleic acid having a sequence set forth as SEQ ID NO: 21. In view of the Applicants' amendments, Applicants respectfully request withdrawal of the Examiner's rejection of Claim 4, under 35 U.S.C. §112, second paragraph.

According to the Examiner, "claim 4 is indefinite because the phrase "fragments of (1) and (2)" is recited in an improper Markush format."

Claim 4 as amended eliminates the phrase "fragments of (1) and (2)," thus obviating the Examiner's rejection. In view of the Applicants' amendments, Applicants respectfully request withdrawal of the Examiner's rejection of Claim 4, under 35 U.S.C. §112, second paragraph.

According to the Examiner, "claim 4 is indefinite because it recites the term "unique," "because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "unique" an artisan cannot determine what additional limitations are placed upon a claim by the presence of this term."

Respectfully, Applicants disagree. The term "unique" refers to a fragment of a nucleic acid molecule of SEQ ID NO:1 between 20 and 3360 nucleotides in length that acts as a signature for the larger LEDGF nucleic acid. As taught in the specification, unique fragments can be used as probes in Southern and Northern blot assays to identify such nucleic acids, or can be used in amplification assays such as those employing PCR. (see at least pages 13, line 13 – page 14, line 25). Those skilled in the art are well versed in methods for selecting such sequences, typically by performing homology searches using an algorithm such as NCBI's BLAST, although, in addition, they may also perform *in vitro* confirmatory hybridization and sequencing analysis. In view of the Applicants' arguments, Applicants respectfully request withdrawal of the Examiner's rejection of Claim 4, under 35 U.S.C. §112, second paragraph.

According to the Examiner, claim 5 recites the limitation "the sequence group."

Claim 4 as amended now gives the limitation "the sequence group" of claim 5, proper antecedent basis, thus rendering the Examiner's rejection moot. In view of the Applicants' amendments, Applicants respectfully request withdrawal of the Examiner's rejection of Claim 5, under 35 U.S.C. §112, second paragraph.

According to the Examiner, "claim 6 is indefinite over the recitation of "the fragment" because the antecedent basis for this limitation is unclear."

Claim 6 as amended introduces the term "unique" prior to "fragment," thus making clear that it refers to "the unique fragment" of claim 4, and rendering the Examiner's rejection moot. In view of the Applicants' amendments, Applicants respectfully request withdrawal of the Examiner's rejection of Claim 6, under 35 U.S.C. §112, second paragraph.

According to the Examiner, "claim 7 is indefinite over the recitation of "encodes a polypeptide, or fragment of, which binds a human antibody" because in view of the use of the indefinite article in the phrase "a polypeptide", the broadest reasonable interpretation of the claim is that it is directed to a nucleic acid molecule encoding a polypeptide corresponding to any contiguous subset of the codons within the nucleic acid molecule," ant that "it is unclear which polypeptide is intended." In addition, the Examiner finds claim 7 as indefinite "over the recitation of "a fragment of" because, according to the Examiner, "the antecedent basis for this limitation is unclear."

Claim 7 as amended now includes language directed to a structural feature of the polypeptide to which a human antibody binds. According to amended claim 7, "the [encoded] polypeptide shares at least 75% amino acid identity to SEQ ID NO.: 2." Thus, it is Applicants' belief that a structural relationship between the human antibody and the exemplified LEDGF (SEQ ID NO.: 2) now exists. In addition, the recitation of "a fragment of" is amended to "a fragment of the polypeptide thereof." In view of the Applicants' amendments, Applicants respectfully request withdrawal of the Examiner's rejection of Claim 7, under 35 U.S.C. §112, second paragraph.

According to the Examiner, "claim 26 is indefinite because it is unclear if the kit or the package contains the nucleic acid.

Claim 26 is amended according to the Examiner's suggestion, and makes clear that it is the package that contains the nucleic acid. In view of the Applicants' amendments, Applicants respectfully request withdrawal of the Examiner's rejection of Claim 26, under 35 U.S.C. §112, second paragraph.

According to the Examiner, "claim 26 is indefinite because it recites the term "selectively binds"."

Claim 26 as amended replaces the language "selectively binds" with "hybridizes," a term commonly used in connection with nucleic acid art. In view of the Applicants' amendments, Applicants

respectfully request withdrawal of the Examiner's rejection of Claim 26, under 35 U.S.C. §112, second paragraph.

Summary

Applicants believe that each of the pending claims is in condition for allowance. Applicants respectfully request that the Examiner telephone the undersigned attorney in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicants' attorney would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (Extension 286).

Respectfully Submitted,

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Date: February 13, 2002
x02/13/02

MARKED-UP CLAIMS

1. (Thrice Amended) An isolated nucleic acid molecule selected from the group consisting of:

(a) a nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of the nucleic acid of SEQ ID NO:1 and which codes for a polypeptide that [induces protein synthesis in an epithelial cell] stimulates the growth of lens epithelial cells, wherein the stringent conditions comprise hybridization at 65°C in hybridization buffer wherein the hybridization buffer comprises [(]3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH_2PO_4(pH7), 0.5% SDS, and 2mM EDTA[), wherein SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid],

(b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and

(c) complements of (a) or (b).

4. (Thrice Amended) An isolated nucleic acid molecule selected from the group consisting of

(c) a unique fragment of a nucleic acid molecule of SEQ ID NO:1 between 20 and 3360 nucleotides in length, and

(d) complements of (a),

provided that the unique fragment includes a sequence of contiguous nucleotides which is not identical to any sequence selected from [the] a sequence group consisting of

(1) SEQ ID NO: [14, 15, 16, or] 21, and

(2) complements of (1),

[(3) fragments of (1) and (2)].

6. (Amended) The isolated nucleic acid molecule of claim 4, wherein the unique fragment has a size selected from the group consisting of at least: [8 nucleotides, 10 nucleotides, 12 nucleotides, 14 nucleotides, 16 nucleotides, 18 nucleotides, 20, nucleotides,] 22 nucleotides, 24 nucleotides, 26 nucleotides, 28 nucleotides, 30 nucleotides, 50 nucleotides, 75 nucleotides, 100 nucleotides, and 200 nucleotides.

7. (Amended) The isolated nucleic acid molecule of claim 4, wherein the molecule encodes a polypeptide [,] or a fragment of the polypeptide thereof[,] which binds a human antibody, wherein the polypeptide shares at least 75% amino acid identity to SEQ ID NO.: 2.

26. (Thrice Amended) A kit[,] comprising a package, wherein the package contains [containing]:

(i) a nucleic acid agent that [selectively binds] hybridizes to [the] an isolated nucleic acid [of claim 1] selected from the group consisting of:

(a) a nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of the nucleic acid of SEQ ID NO:1 and which codes for a polypeptide that stimulates the growth of lens epithelial cells, wherein the stringent conditions comprise hybridization at 65°C in hybridization buffer wherein the hybridization buffer comprises 3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH_2PO_4(pH7), 0.5% SDS, and 2mM EDTA,

(b) nucleic acid molecules that differ from the nucleic acid molecules of (a) in codon sequence due to the degeneracy of the genetic code, and

(c) complements of (a) or (b),

and

(ii) a control comprising an amount of an isolated nucleic acid as in any one of claims 1 or 4 for comparing to a measured value of [binding] hybridization of said nucleic acid agent to said isolated nucleic acid [of claim 1] in (i).

MARKED-UP SPECIFICATION (page 12)

sulphate; and EDTA is ethylenediaminetetracetic acid. After hybridization, the membrane upon which the DNA is transferred is washed at 2 x SSC at room temperature and then at 0.1 x SSC/0.1 x SDS at temperatures up to 68°C.

There are other conditions, reagents, and so forth which can be used, and would result in a similar degree of stringency. The skilled artisan will be familiar with such conditions, and thus they are not given here. It will be understood, however, that the skilled artisan will be able to manipulate the conditions in a manner to permit the clear identification of homologs and alleles of LEDGF nucleic acids of the invention. The skilled artisan also is familiar with the methodology for screening cells and libraries for expression of such molecules which then are routinely isolated, followed by isolation of the pertinent nucleic acid molecule and sequencing.

In general homologs and alleles typically will share at least 40% nucleotide identity and/or at least 50% amino acid identity to SEQ ID NO:1 and SEQ ID NO:2, respectively, in some instances will share at least 50% nucleotide identity and/or at least 65% amino acid identity and in still other instances will share at least 60% nucleotide identity and/or at least 75% amino acid identity. The homology can be calculated using various, publicly available software tools developed by NCBI (Bethesda, Maryland) that can be obtained through the internet [(ftp:/ncbi.nlm.nih.gov/pub/)]. Exemplary tools include the BLAST system [available at http://wwww.ncbi.nlm.nih.gov]. Pairwise and ClustalW alignments (BLOSUM30 matrix setting) as well as Kyte-Doolittle hydropathic analysis can be obtained using the MacVetor sequence analysis software (Oxford Molecular Group). Watson-Crick complements of the foregoing nucleic acids also are embraced by the invention.

In screening for LEDGF related genes, such as homologs and alleles of LEDGF, a Southern blot may be performed using the foregoing conditions, together with a radioactive probe. After washing the membrane to which the DNA is finally transferred, the membrane can be placed against X-ray film or a phosphoimager plate to detect the radioactive signal.

Given that the expression of the LEDGF gene is abundant in certain human tissues, and given the teachings herein of a full-length human LEDGF cDNA clone, other mammalian sequences such as the mouse cDNA clone corresponding to the human LEDGF gene can be